National Research Council

"Available consumption data and current population and fertility rates indicate that over 60,000 newborns annually {in the US} might be at risk for adverse neurodevelopmental effects from *in utero* exposure to MeHg {from fish consumption}"

Toxicological Effects of Methylmercury p325, 2000

No explanation of the basis for this statement was provided

MeHg POISONING EPISODES

- 1953 Sweden - Treated grain
- 1958 Minamata - Industrial pollution
- 1965 Niigata - Industrial pollution
- 1971 Iraq - Treated grain
- 1972 New Mexico - Treated grain

← Yudo

T.H. 65y

Lives on Minamata Bay

MeHg Poisoning

Japan

From Eugene Smith's Photo Essay Minamata

Minamata Disease Clinical Findings

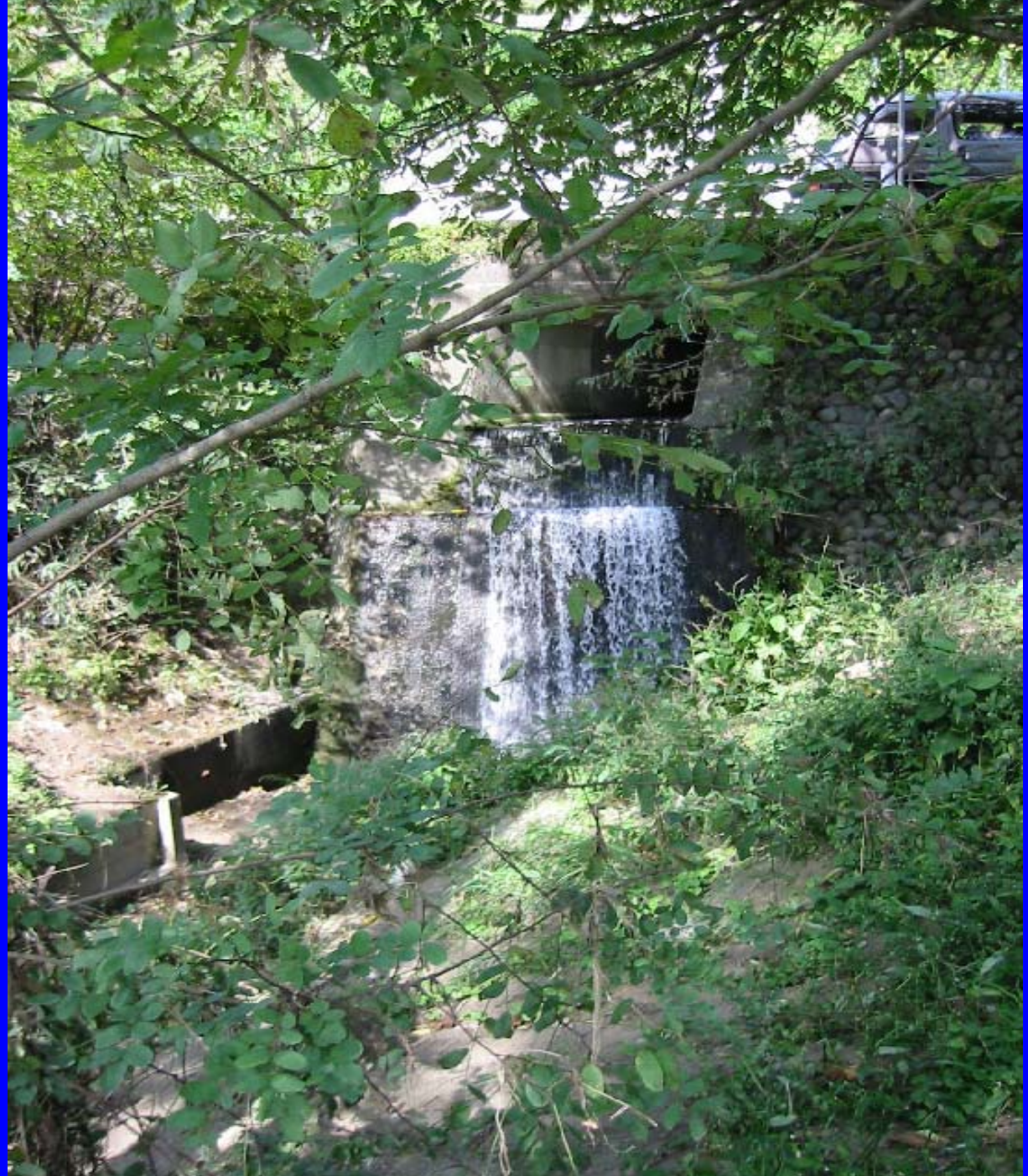
- Mental retardation
- Cerebral palsy (extrapyramidal)
- Microcephaly
- Ataxia (dysarthria, cerebellar signs)
- Strabismus
- Seizures

Japan

From Eugene Smith's Photo Essay Minamata

Waste outlet
Showa Denka
Plant

Kanasa on Agano
River 2002

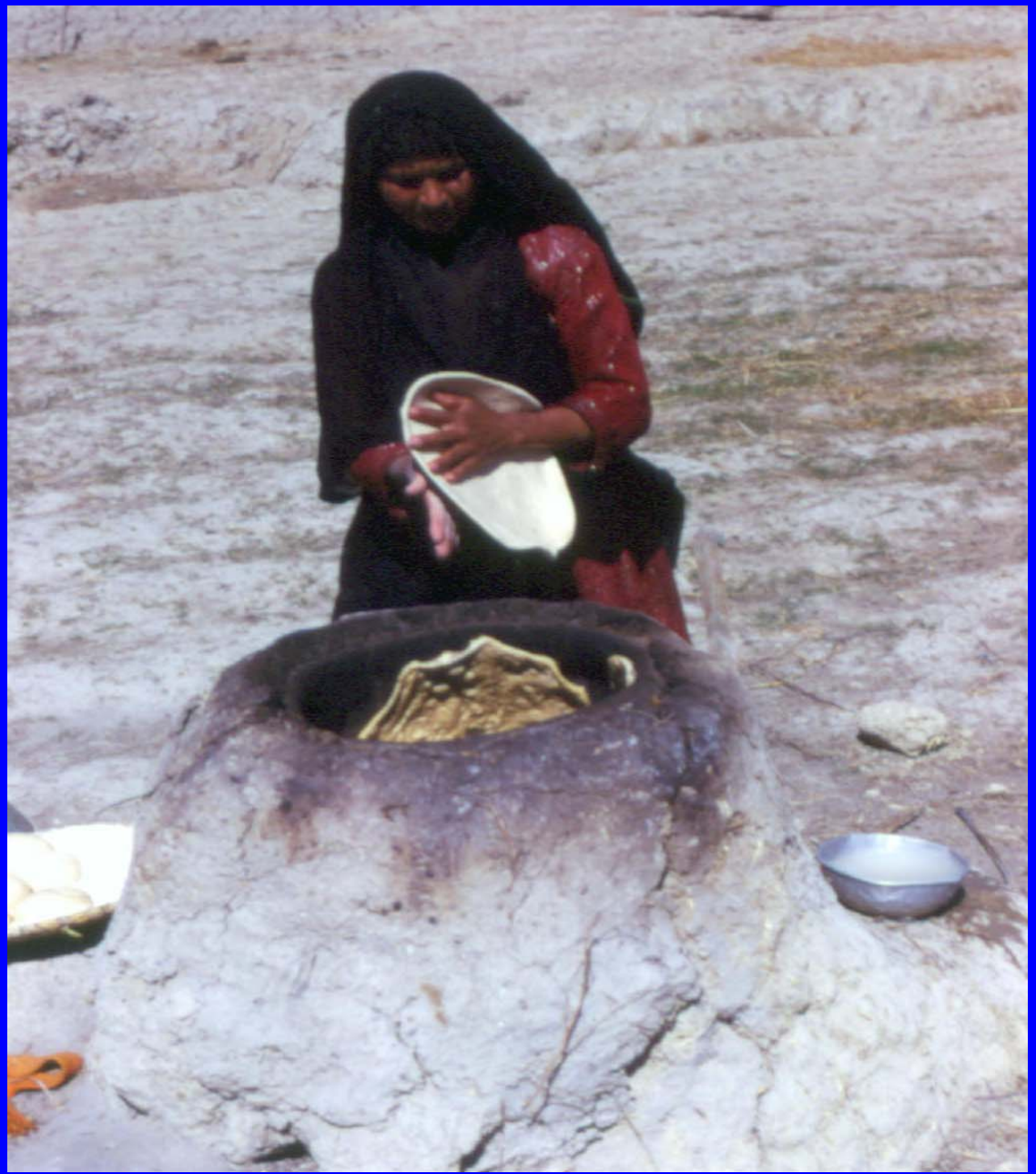


C.F. 37 y/o
Niigata

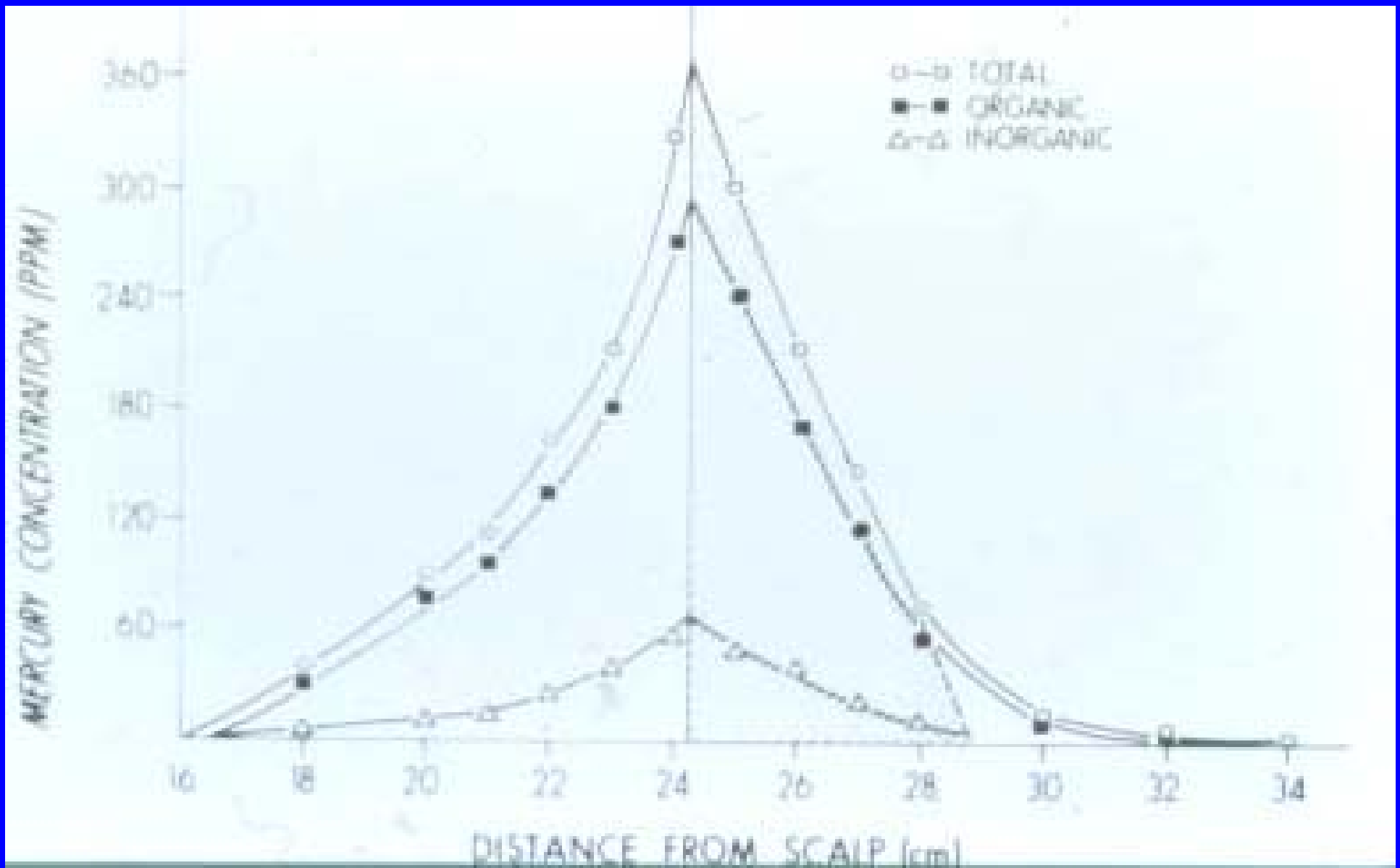
Congenital MeHg
Poisoning.

Mother with only
Sensory disturbance.
Mom hair 293 ppm

Cannot speak
writes fairly well
Cooks
Dystonic CP



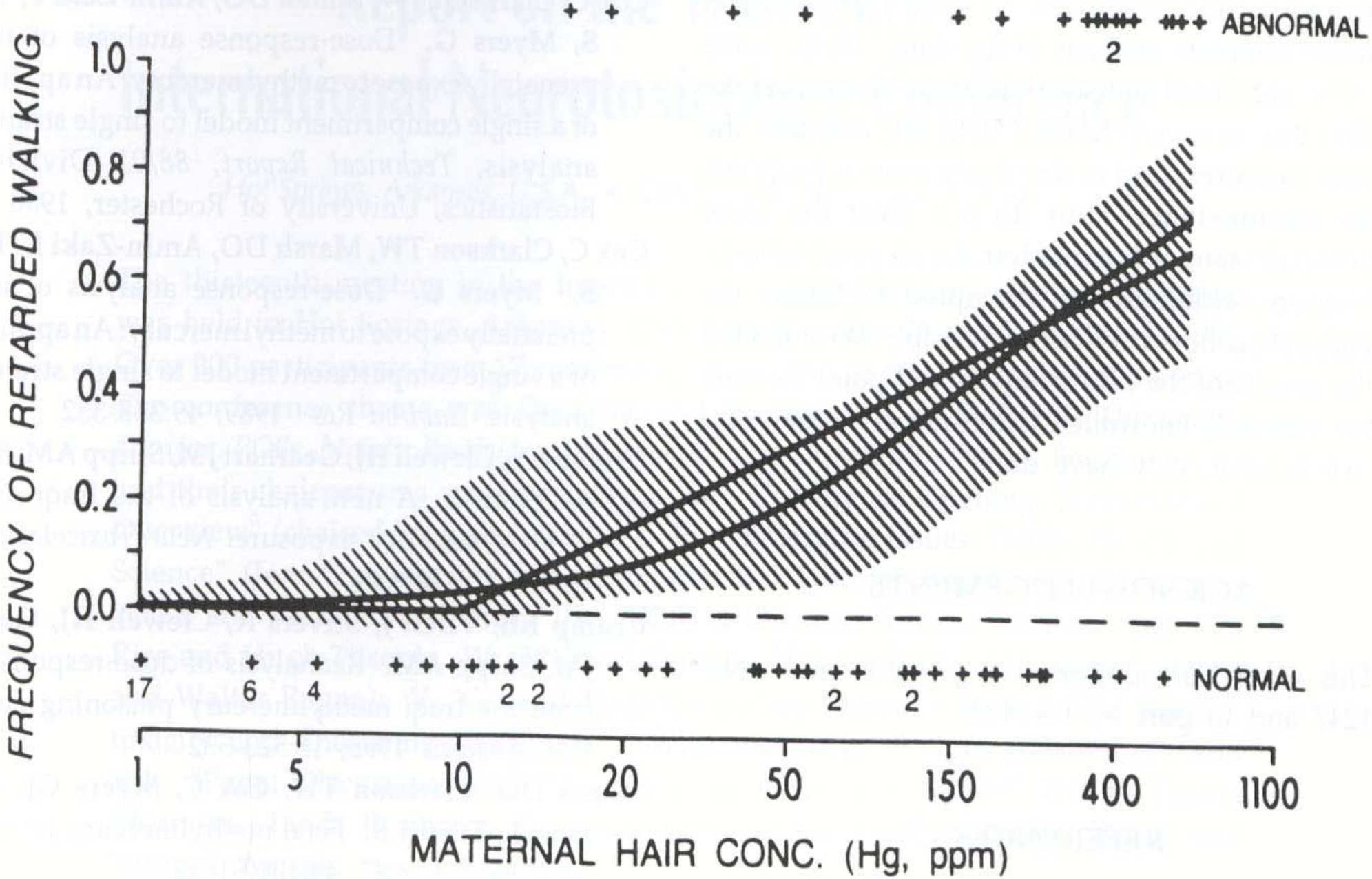
Iraq
1973



Iraq – Maternal Hair

Dr. Marsh examining child in Iraq 1973

Cox et al., Environ Res 1989



Hypothesis

- Exposure to MeHg from fish consumption during pregnancy could be associated with subtle adverse neurodevelopmental outcomes in children.

People Depending on Fish for Protein

- 1 Billion in Asia
  - Japanese consume 1/5 of all fish caught
- 1 in 5 in Africa

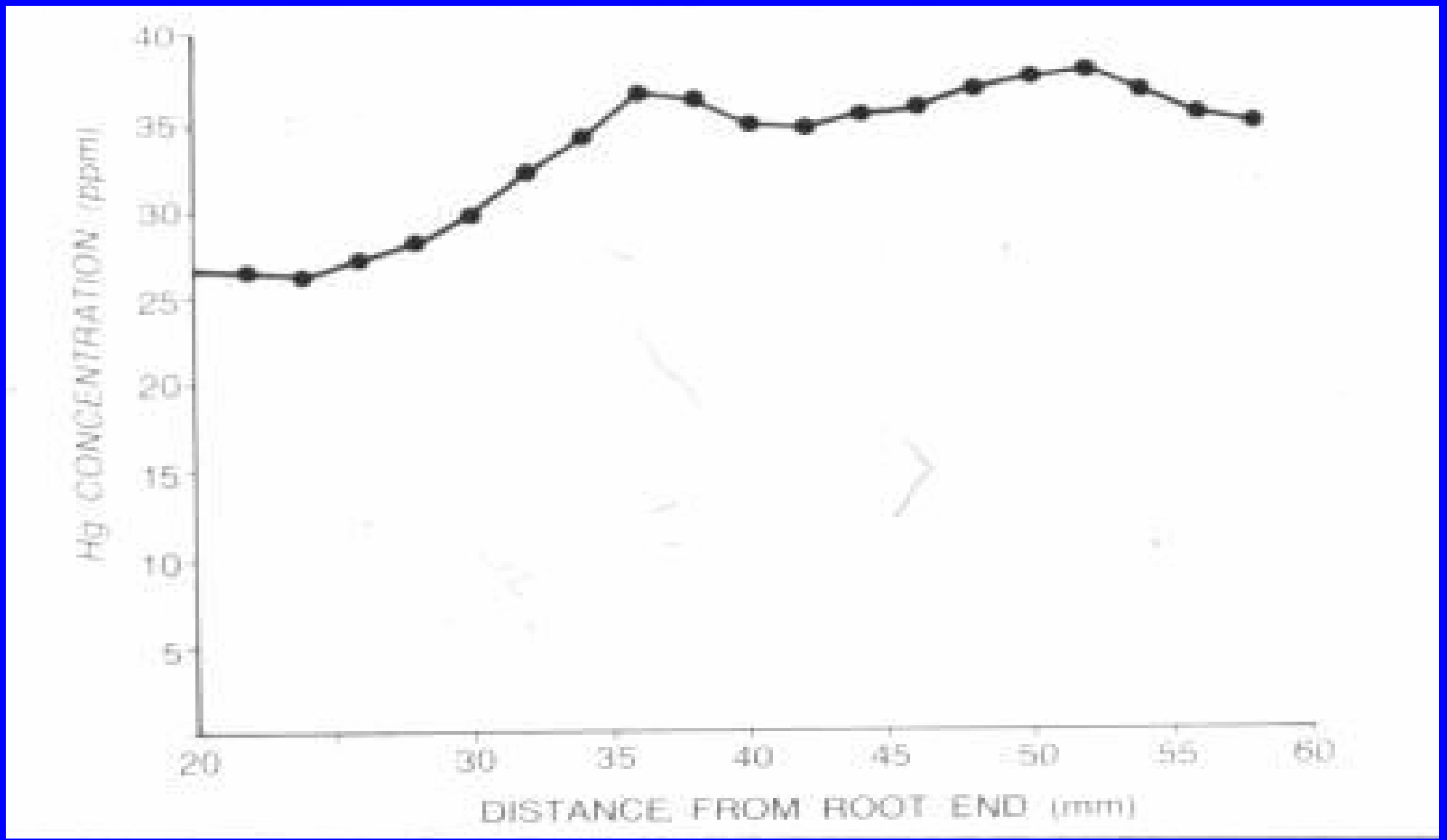
From the Discovery Channel, 2002

Epidemiology Studies of Fish Consumption

- 1984 New Zealand — fish (max 4.4)
- 1936 Canada — fish (max 27)
- 1995 Peru — fish
- 1995 Seychelles — fish
- 1997 Faeroes — whale & fish

Epidemiology Studies of Fish Consumption

Study	N	Age	Max Hg ppm
NZ	64	4-6y	19 (86)
Canada	215	12-30m	23
Peru	131	?	30
Seychelles	740	.5-9y	27
Faeroes	915	7.5y	>10 (91)



SCDS – Maternal Hair

Epidemiology Studies of Fish Consumption

Study	Associations (Hg & outcome)
NZ*	DDST, TOLD, WISC (2), MCSA (2)
Canada	Neuro exam (males only), not DDST
Peru	None
Seychelles	None (5 evaluations to 107 mo)
Faeroes	FT, CPT, WISC–DS, BNT, CVLT

* Associations found only by omitting child with 86 ppm exposure

New Zealand

- Small N in case control study
- Mismatching
  - ethnicity testing times
- Association of test results best with
  - child's ethnic background & social class
- Maternal covariates omitted
  - intelligence education

New Zealand

- Reanalysis 1998 – Crump
- Associations with Hg exposure
- - TOLD
- - WISC - Full Scale IQ & Perceptual Perf
- - MSCA – Motor Scale & Perceptual Perf

Φ Present only when highest value (86 ppm) dropped

Low dose MeHg exposure
Canadian study

- 243 Cree Indian children
- Association with abnormal muscle tone and DTRs
  - Present only in males

Canada

- Neurological abnormalities differed from effects previously described
- Neurological abnormality associated with mercury was non-physiologic
  - DTRs either increased or decreased
- No consistent dose response relationship
- 4 Pediatric Neurologists

Faeroe Islands

- Cohort = 915
- Exposure from whale meat / blubber
  - Episodic Hg (3 ppm) - PCB high
- Examined age 7 years
- Extensive test battery – 4 hours
- Statistical association with tests of
  - language - attention - memory
  - visual perception - motor skills


Paris
Rome
Cairo
Alexandria
Victoria
SEYCHELLES
Mahé
Amirante Is. (Seychelles)
Aldabra Is. (Seychelles)
Providence I.(Seychelles)
Farquhar Is. (Seychelles)
Agalega Is. (Mauritius)
Coetivy Is. (Seychelles)
Cargados Carajos (Mauritius)
Tromelin (Fr.)
Mauritius
Rodriguez I. (Mauritius)
Réunion (Fr.)
Scale
500
0
500
0
Where is Seychelles?
Modified Gall Projection


Fish Market Seychelles

Testing Design

SCDS MAIN STUDY
RESULTS 6 mo

- DDST-R
  - Small number of abnormal or questionable scores
    - no analysis possible
- Neurological examination
  - Overall neurological - small number of abnormal exams
    - no analysis possible
  - DTR's - no mercury effect
  - Limb tone - no mercury effect
    - associated with gender (M), maternal education, and birth weight

SCDS MAIN STUDY RESULTS 19 & 29 mo

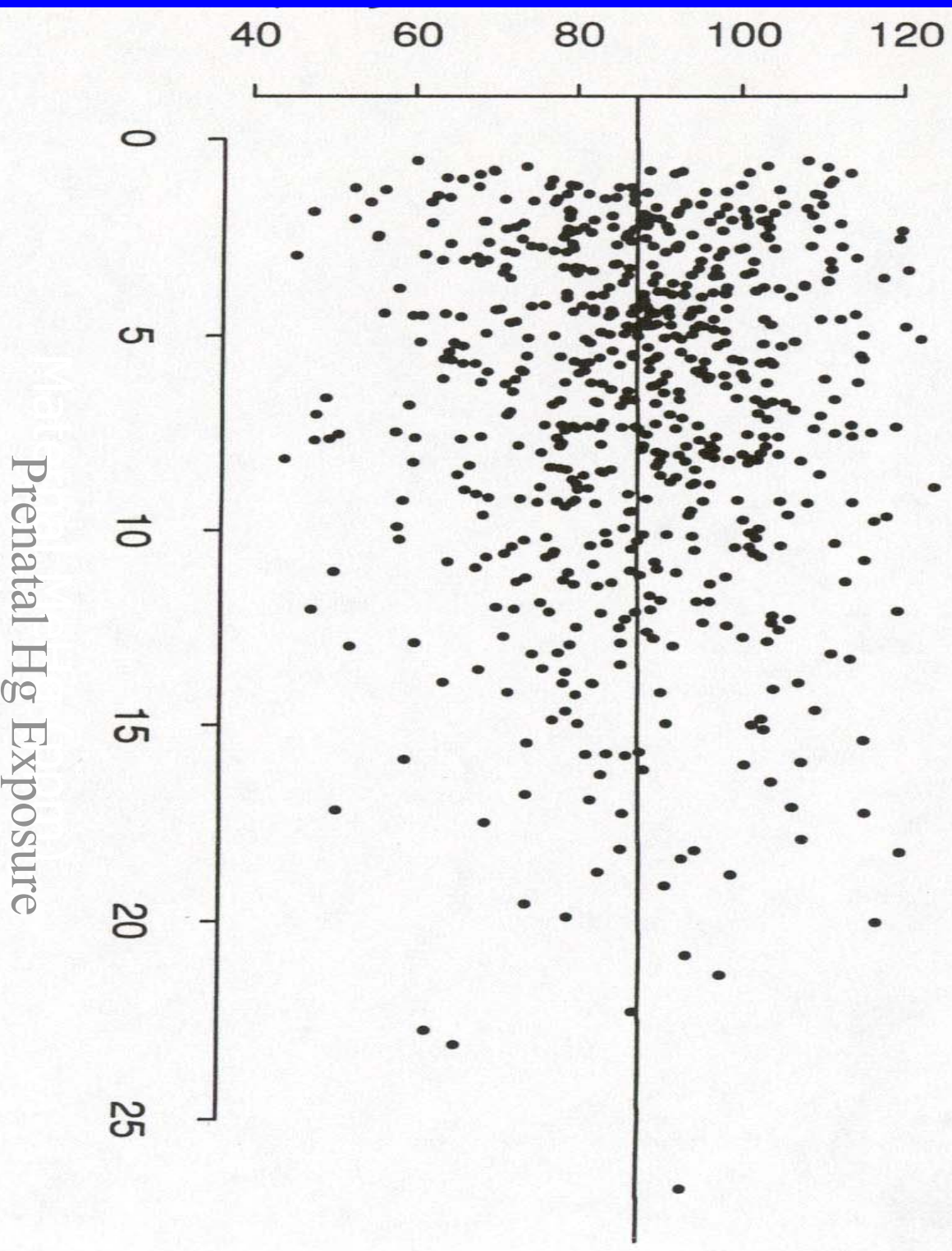
- BSID-MDI - mean 19m = 97, 29m = 100
  - no association with Hg
- BSID-PDI - mean 19m = 126, 29m = 121
  - no association with Hg
- Infant behavior record (6 items)
  - activity associated with Hg (as Hg increased, activity decreased in males only)

SCDS Main Study Results 66 mo

Endpoint	Prenatal	Postnatal
MSCA GCI	NS	NS
PLS	+	+
Bender - errors	NS	+ males
W-J Applied Problems	NS	+
W-J Letter Word	NS	NS
CBCL	NS	NS

Davidson et al., JAMA 1998

Woodcock-Johnson Applied Problems Score (Adjusted for Covariates) 5.5 y



SCDS Main Study Results 107 mo

- Expected effects of co-variates
- Modest R^2s
- endpoints (21) associations
  - one adverse
  - one beneficial

Congenital MeHg Poisoning

Country	# Pts	Exposure – Mat hair ppm
USA	1	Unknown (sibs >1000)
Minamata	>100	Unknown
Niigata	1	293 (13 with 50-115 N)
Iraq		
– Choi	2	181, 297
– Marsh	6	404, 405, 418, 443, 468, 598
Φ 21 mothers >200 ppm		
– Amin-Zaki	15	32 – 532 (most >100)

Recommended Maximum MeHg Exposure in ug/kg/d

Agency	Rfd ug/k/d	hair ppm	blood ppb
US EPA	0.1	1	4-5
ATSDR	0.3	3	12-15
FDA	0.4	4	16-20
WHO	0.5	5	20-24

Derivation of 60,000 statement*

- Assume EPA Rfd of 0.1 ug/kg/d is correct
- US population of women 15-44 y 60,208,000
- 30% reported fish consumption 18,363,440
- 5% reported consuming >100 g/d 918,172
- Birth rate for women 15-44 y in US 65.6/1000
- Newborns at high risk annually 60,232

*Letter from chair of NAS 12/6/00 explaining derivation


Epidemiology can only quantify a
risk, not prove its absence